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Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M Street., S.W.
Washington, D.C. 20460
Attn: Section 8(e) Coordinator (CAP Agreement)

Dear Coordinator:

8ECAP-0025

On behalf of the Regulatee and pursuant to Unit II B.1.b. and Unit II C of the 6/28/91CAP Agreement, E.I. Du Pont de Nemours and Co. hereby submits (*in triplicate*) the attached studies. Submission of this information is voluntary and is occasioned by unilateral changes in EPA's standard as to what EPA now considers as reportable information. Regulatee's submission of information is made solely in response to the new EPA §8(e) reporting standards and is not an admission: (1) of TSCA violation or liability; (2) that Regulatee's activities with the study compounds reasonably support a conclusion of substantial health or environmental risk or (3) that the studies themselves reasonably support a conclusion of substantial health or environmental risk.

The "Reporting Guide" creates new TSCA 8(e) reporting criteria which were not previously announced by EPA in its 1978 Statement of Interpretation and Enforcement Policy, 43 Fed Reg 11110 (March 16, 1978). The "Reporting Guide states criteria which expands upon and conflicts with the 1978 Statement of Interpretation. Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" raises significant due processes issues and clouds the appropriate reporting standard by which regulated persons can assure TSCA Section 8(e) compliance.

For Regulatee,

Mark H. Christman
Counsel
Legal D-7158
1007 Market Street
Wilmington, DE 19898
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2/22/95

ATTACHMENT 1

Submission of information is made under the 6/28/91 CAP Agreement, Unit II. This submission is made voluntarily and is occasioned by recent changes in EPA's TSCA §8(e) reporting standard; such changes made, for the first time in 1991 and 1992 without prior notice and in violation of Regulatee's constitutional due process rights. Regulatee's submission of information under this changed standard is not a waiver of its due process rights; an admission of TSCA violation or liability, or an admission that Regulatee's activities with the study compounds reasonably support a conclusion of substantial risk to health or to the environment. Regulatee has historically relied in good faith upon the 1978 Statement of Interpretation and Enforcement Policy criteria for determining whether study information is reportable under TSCA §8(e), 43 Fed Reg 11110 (March 16, 1978). EPA has not, to date, amended this Statement of Interpretation.

After CAP registration, EPA provided the Regulatee the June 1, 1991 "TSCA Section 8(e) Reporting Guide". This "Guide" has been further amended by EPA, EPA letter, April 10, 1992. EPA has not indicated that the "Reporting Guide" or the April 1992 amendment supersedes the 1978 Statement of Interpretation. The "Reporting Guide" and April 1992 amendment substantively lowers the Statement of Interpretation 's TSCA §8(e) reporting standard[2]. This is particularly troublesome as the "Reporting Guide" states criteria, applied retroactively, which expands upon and conflicts with the Statement of Interpretation.[3] Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" and the April 1992 amendment clouds the appropriate standard by which regulated persons must assess information for purposes of TSCA §8(e).

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[2]In sharp contrast to the Agency's 1977 and 1978 actions to soliciting public comment on the proposed and final §8(e) Policy, EPA has unilaterally pronounced §8(e) substantive reporting criteria in the 1991 Section 8(e) Guide without public notice and comment, See 42 Fed Reg 45362 (9/9/77), "Notification of Substantial Risk under Section 8(e): Proposed Guidance".

[3]A comparison of the 1978 Statement of Interpretation and the 1992 "Reporting Guide" is a appended.

Throughout the CAP, EPA has mischaracterized the 1991 guidance as reflecting "longstanding" EPA policy concerning the standards by which toxicity information should be reviewed for purposes of §8(e) compliance. Regulatee recognizes that experience with the 1978 Statement of Interpretation may cause a review of its criteri. Regulatee supports and has no objection to the Agency's amending reporting criteria *provided that* such amendment is not applied to the regulated community in an unfair way. However, with the unilateral announcement of the CAP under the auspices of an OCM enforcement proceeding, EPA has wrought a terrific unfairness since much of the criteria EPA has espoused in the June 1991 Reporting Guide and in the Agency's April 2, 1992 amendment is new criteria which does not.exist in the 1978 Statement of Interpretation and Enforcement Policy.

The following examples of new criteria contained in the "Reporting Guide" that is not contained in the Statement of Interpretation follow:

- o even though EPA expressly disclaims each "status report" as being preliminary evaluations that should not be regarded as final EPA policy or intent[4], the "Reporting Guide" gives the "status reports" great weight as "sound and adequate basis" from which to determine mandatory reporting obligations. ("Guide" at page 20).
- o the "Reporting Guide" contains a matrix that establishes new numerical reporting "cutoff" concentrations for acute lethality information ("Guide" at p. 31). Neither this matrix nor the cutoff values therein are contained in the Statement of Interpretation. The regulated community was not made aware of these cutoff values prior to issuance of the "Reporting Guide" in June, 1991.
- othe "Reporting Guide" states new specific definitional criteria with which the Agency, for the first time, defines as 'distinguishable neurotoxicological effects'; such criteria/guidance not expressed in the 1978 Statement of Interpretation.[5];

- othe "Reporting Guide" provides new review/ reporting criteria for irritation and sensitization studies; such criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.
- othe "Reporting Guide" publicizes certain EPA Q/A criteria issued to the Monsanto Co. in 1989 which are not in the Statement of Interpretation; have never been published in the Federal Register or distributed by the EPA to the Regulatee. Such Q/A establishes new reporting criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy .

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[4]The 'status reports' address the significance, if any, of particular information reported to the Agency, rather than stating EPA's interpretation of §8(e) reporting criteria. In the infrequent instances in which the status reports contain discussion of reportability, the analysis is invariably quite limited, without substantial supporting scientific or legal rationale.

[5] *See, e.g,* 10/2/91 letter from Du Pont to EPA regarding the definition of 'serious and prolonged effects' as this term may relate to transient anesthetic effects observed at lethal levels; 10/1/91 letter from the American Petroleum Institute to EPA regarding clarification of the Reporting Guide criteria.

In discharging its responsibilities, an administrative agency must give the regulated community fair and adequate warning to as what constitutes noncompliance for which penalties may be assessed.

> Among the myriad applications of the due process clause is the fundamental principle that statutes and regulations which purport to govern conduct must give an adequate warning of what they command or forbid.... Even a regulation which governs purely economic or commercial activities, if its violation can engender penalties, must be so framed as to provide a constitutionally adequate warning to those whose activities are governed.

Diebold, Inc. v. Marshall, 585 F.2d 1327, 1335-36 (D.C. Cir. 1978). *See also*, Rollins Environemntal Services (NJ) Inc. v. U.S. Environmental Protection Agency, 937 F. 2d 649 (D.C. Cir. 1991).

While neither the are rules, This principle has been applied to hold that agency 'clarification', such as the Statement of Interpretation, the "Reporting Guide" nor the April 1992 amendments will not applied retroactively.

> ...a federal court will not retroactively apply an unforeseeable interpretation of an administrative regulation to the detriment of a regulated party on the theory that the post hoc interpretation asserted by the Agency is generally consistent with the policies underlying the Agency's regulatory program, when the semantic meaning of the regulations, as previously drafted and construed by the appropriate agency, does not support the interpretation which that agency urges upon the court.

Standard Oil Co. v. Federal Energy Administration, 453 F. Supp. 203, 240 (N.D. Ohio 1978), aff'd sub nom. Standard Oil Co. v. Department of Energy, 596 F.2d 1029 (Em. App. 1978):

The 1978 Statement of Interpretation does not provide adequate notice of, and indeed conflicts with, the Agency's current position at §8(e) requires reporting of all 'positive' toxicological findings without regard to an assessment of their relevance to human health. In accordance with the statute, EPA's 1978 Statement of Interpretation requires the regulated community to use scientific judgment to evaluate the significance of toxicological findings and to determining whether they reasonably support a conclusion of a substantial risk. Part V of the Statement of Interpretation urges persons to consider "the fact or probability" of an effect's occurrence. Similarly, the 1978 Statement of Interpretation stresses that an animal study is reportable only when "it contains reliable evidence ascribing the effect to the chemical." 43 Fed Reg. at 11112. Moreover, EPA's Statement of Interpretation defines the substantiality of risk as a function of both the seriousness of the effect and the probability of its occurrence. 43 Fed Reg 11110 (1978). Earlier Agency interpretation also emphasized the "substantial" nature of a §8(e) determination. See 42 Fed Reg 45362, 45363

(1977). [Section 8(e) findings require "extraordinary exposure to a chemical substance...which critically imperil human health or the environment"].

The recently issued "Reporting Guide" and April 1992 Amendment guidance requires reporting beyond and inconsistent with that required by the Statement of Interpretation. Given the statute and the Statement of Interpretation's explicit focus on substantial human or environmental risk, whether a substance poses a "substantial risk" of injury requires the application of scientific judgment to the available data on a case-by-case basis.

If an overall weight-of-evidence analysis indicates that this classification is unwarranted, reporting should be unnecessary under §8(e) because the available data will not "reasonably support the conclusion" that the chemical presents a substantial risk of serious adverse consequences to human health.

Neither the legislative history of §8(e) nor the plain meaning of the statute support EPA's recent lowering of the reporting threshold that TSCA §8(e) was intended to be a sweeping information gathering mechanism. In introducing the new version of the toxic substances legislation, Representative Eckhart included for the record discussion of the specific changes from the version of H. R. 10318 reported by the Consumer Protection and Finance Subcommittee in December 1975. One of these changes was to modify the standard for reporting under §8(e). The standard in the House version was changed from "causes or contributes to an unreasonable risk" to "causes or significantly contributes to a substantial risk". This particular change was one of several made in TSCA §8 to avoid placing an undue burden on the regulated community. The final changes to focus the scope of Section 8(e) were made in the version reported by the Conference Committee.

The word "substantial" means "considerable in importance, value, degree, amount or extent". Therefore, as generally understood, a "substantial risk" is one which will affect a considerable number of people or portion of the environment, will cause serious injury and is based on reasonably sound scientific analysis or data. Support for the interpretation can be found in a similar provision in the Consumer Product Safety Act. Section 15 of the CPSA defines a "substantial product hazard" to be:

> "a product defect which because of the pattern of defect, the number of defective products distributed in commerce, the severity of the risk, or otherwise, creates a substantial risk of injury to the public."

Similarly, EPA has interpreted the word 'substantial' as a quantitative measurement. Thus, a 'substantial risk' is a risk that can be quantified, *See,* 56 Fed Reg 32292, 32297 (7/15/91). Finally, since information pertinent to the exposure of humans or the environment to chemical substances or mixtures may be obtained by EPA through Sections 8(a) and 8(d) regardless of the degree of potential risk, §8(e) has specialized function. Consequently, information subject to §8(e) reporting should be of a type which would lead a reasonable man to conclude that some type action was required immediately to prevent injury to health or the environment.

Attachment

Comparison:

Reporting triggers found in the 1978 "Statement of Interpretation/ Enforcement Policy",43 Fed Reg 11110 (3/16/78) and the June 1991 *Section 8(e) Guide.*

TEST TYPE	1978 POLICY CRITERIA EXIST?	New 1991 GUIDE CRITERIA EXIST?
ACUTE LETHALITY		
Oral	N}	Y}
Dermal	N}	Y}
Inhalation (Vapors)	}[6]	}[7]
aerosol	N}	Y}
dusts/ particles	N}	Y}
SKIN IRRITATION	N	Y[8]
SKIN SENSITIZATION (ANIMALS)	N	Y[9]
EYE IRRITATION	N	Y[10]
SUBCHRONIC (ORAL/DERMAL/INHALATION)	N	Y[11]
REPRODUCTION STUDY	N	Y[12]
DEVELOPMENTAL TOX	Y[13]	Y[14]

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[6] 43 Fed Reg at 11114, comment 14:

"This policy statements directs the reporitng of specifiec effects when unknown to the Administrator. Many routine tests are based on a knowledge of toxicity associated with a chemicalL unknown effects occurring during such a range test may have to be reported if they are those of concern tot he Agency and if the information meets the criteria set forth in Parts V and VII."

[7] Guide at pp.22, 29-31.

[8] Guide at pp-34-36.

[9] Guide at pp-34-36.

[10] Guide at pp-34-36.

[11] Guide at pp-22; 36-37.

[12] Guide at pp-22

[13] 43 Fed Reg at 11112

"Birth Defects" listed.

[14] Guide at pp-22

NEUROTOXICITY	N	Y[15]
CARCINOGENICITY	Y[16]	Y[17]
MUTAGENICITY		
In Vitro	Y}[18]	Y} [19]
In Vivo	Y}	Y}
ENVIRONMENTAL		
Bioaccumulation	Y}	N
Bioconcentration	Y}[20]	N
Oct/water Part. Coeff.	Y}	N
Acute Fish	N	N
Acute Daphnia	N	N
Subchronic Fish	N	N
Subchronic Daphnia	N	N
Chronic Fish	N	N
AVIAN		
Acute	N	N
Reproductive	N	N
Reprodcutive	N	N

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[15] Guide at pp-23; 33-34.

[16] 43 Fed Reg at 11112
"Cancer" listed

[17] Guide at pp-21.

[18] 43 Fed Reg at 11112; 11115 at Comment 15
"Mutagenicity" listed/ *in vivo* vs *invitro* discussed; discussion of "Ames test".

[19] Guide at pp-23.

[20] 43 Fed Reg at 11112; 11115 at Comment 16.

CAS # 822-06-0
Chem: Hexamethylene diisocyanate
Title: Evaluation of the toxicity of hexamethylene diisocyanate (HDI) relative to that of toluene-2,4-diisocyanate (TDI)
Date: 3/16/61
Summary of Effects: Skin sensitization

EVALUATION OF THE TOXICITY OF HEXAMETHYLENE DIISOCYANATE (HDI) RELATIVE TO THAT OF TOLUENE-2,4-DIISOCYANATE (TDI)

Medical Research Project No. MR-526

Report No. 9-61

INTRODUCTION

Extensive toxicity tests run previously at Haskell Laboratory and reported by John A. Zapp, Jr.[1] indicated that toluene-2,4-diisocyanate (TDI) had a low order of acute oral toxicity, was moderately toxic by inhalation, was very irritating to skin and mucous membranes, and caused skin sensitization. In addition, asthmatic reactions have been reported in men exposed to TDI and other organic isocyanates.[2,3,4] Pertinent animal toxicity data from the above report, amended on the basis of more recent data, are summarized in Table I.

Earlier work reported by M. W. Goldblatt of Imperial Chemical Industries, Limited,[5] had indicated that hexamethylene diisocyanate (HDI) was more toxic to mice orally and by skin absorption, and was more irritating to the skin of mice and eyes of rabbits than were the aromatic diisocyanates, methylene bis (4-phenyl isocyanate) (MDI), and m-phenylene diisocyanate (PDI). Further evidence for the greater oral toxicity of HDI relative to an aromatic diisocyanate was provided by early work at Haskell Laboratory, reported in 1946.[6] The oral ALD for rats for HDI was found to be 0.94 g/kg of body weight, whereas rats survived doses as high as 4.79 g/kg of methylene bis (4-phenyl isocyanate) (MDI) with no apparent ill effects.

Currently, HDI, an aliphatic diisocyanate, is of interest for potential use similar to that of TDI, i.e., as a monomer in the production of polyurethane plastic foams. Accordingly, comparison of the toxicity of HDI with that of TDI was requested by the Elastomers Department.

The following toxicity tests were carried out with HDI: single and repeated oral and inhalation; skin irritation and sensitization; and eye irritation. In addition, tests were carried out on dogs to determine the inhalation threshold of irritation.

SAMPLES

The following samples were provided by the Elastomers Department to conduct these tests:

Haskell No.	Elastomers Code	Material
2609I	LRP-114	1,6-Hexamethylene Diisocyanate
2608II	LRP-114-A	"
2652	LRP-114-B	"
2724		"
2639	LRP-115	Toluene-2,4-Diisocyanate

ORAL TOXICITY

A. Acute

HDI, undiluted or as solution in peanut oil, was administered by stomach tube to male albino ChR-CD rats, in single doses from 12 to 3400 mg/kg of body weight, one rat per dose level, with a factor of 1.5 between dose levels. The approximate lethal dose (ALD) was found to be 1500 mg/kg of body weight. Animals receiving 3400, 2250, and 1500 mg/kg died within 2 to 21 hours. Prior to death, these animals developed pallor, cyanosis, slow and deep breathing, and diarrhea. Gross autopsy and microscopic examination of tissues failed to reveal the cause of death.

Rats receiving high sublethal doses of 1000 and 670 mg/kg lost weight initially. They, as well as those receiving 450 and 300 mg/kg, had slowed respiration after dosing, and animals at dose levels as low as 40 mg/kg showed evidence of diarrhea. At sacrifice 9 to 12 days after treatment, rats receiving doses as low as 60 mg/kg showed inflammation of the stomach mucosa which, at 1000 and 300 mg/kg, included areas of ulceration. No other lesions attributable to the test material were found.

B. Subacute

HDI as a five per cent solution in peanut oil was administered by stomach tube daily for ten days over a two-week period at a dose level of 300 mg/kg to six male albino ChR-CD rats. Although the rats showed diarrhea and salivation, and appeared uncomfortable after most treatments, they survived. During the first week, weight losses were observed consistently in all animals; however, the average loss of the group on any one day did not exceed that observed in 1 rat following a single dose of 300 mg/kg. During the second week, there were sporadic weight losses, but most animals gained weight. High water consumption was also noted in the treated rats during the second week. Three rats were chosen at random for sacrifice four hours after the tenth treatment, and three were kept for a ten-day observation period, during which no clinical signs of toxicity were observed. Gross and microscopic examination of tissues from these rats revealed an ulcerative gastritis in rats sacrificed the tenth treatment day, and healing gastritis in rats sacrificed ten days later.

SKIN IRRITATION AND SENSITIZATION

When HDI, either undiluted or as 25 or 5 per cent solutions in 1:1 acetone-dioxane containing 13 per cent guinea pig fat, was applied to intact skin of adult male albino guinea pigs, it produced severe erythema and edema, which in the case of the undiluted material resulted in necrosis. When the concentration was lowered to 0.5 per cent, HDI caused moderate irritation to intact skin, and at 0.05 per cent, produced no irritation.

Nine applications of 0.5 to 0.05 per cent solutions to abraded skin over a period of three weeks were followed by a three-week rest period. Challenge tests at the end of the rest period showed that 8/9 guinea pigs had developed allergic contact dermatitis.

EYE IRRITATION

0.1 ml of the undiluted liquid was instilled into both eyes of a male albino rabbit. One eye (left) was washed 20 seconds later with large amounts of water, whereas the other eye (right) was not washed.

Initially, the exposure caused severe conjunctival inflammation accompanied by serous and hemorrhagic exudates of both eyes and severe or moderate corneal injury to the unwashed and washed eyes respectively. When the rabbit was sacrificed eight days after treatment, the corneas of both eyes, on gross examination, appeared dull, and the eyelids were inflamed and still showed the hemorrhagic and serous exudates.

Microscopic examination of the eyes removed at autopsy revealed healed corneal lesions of both eyes and inflammation of the eyelids of the unwashed eye.

INHALATION

A. Acute

Male albino ChR-CD rats were exposed, four at a time, for four or eight hours, in a glass bell jar, to several concentrations of HDI vapor. The vapor was generated by passing a dried air stream of two liters per minute through a bubbler containing a weighed amount of the material. Nominal concentration was calculated on the basis of weight loss of HDI and total air flow during the exposure.

When rats were exposed in this manner to vapor (370 ppm nominal concentration) from a bubbler of HDI warmed with a heating tape to 40-50°C, they died within two to three hours of exposure. During the first half-hour of exposure, the temperature inadvertently overshot to about 180°C, and rats were exposed to an unidentified gray particulate. Prior to death, rats showed signs of irritation, gasping and convulsions. Examination of the tissues showed tracheitis, pleural effusion, and small areas of pulmonary hemorrhage, none of which, however, was considered extensive enough to cause death.

Rats survived four-hour exposure to vapor (72 ppm, nominal; no particulate observed) from a bubbler heated in a 40°C water bath, but showed severe respiratory impairment, cyanosis and signs of irritation during exposure. The respiratory impairment was initially characterized by a hesitancy of the rats to inhale. This progressed to labored breathing and gasping during the exposure. Respiratory impairment continued through the observation period, along with severe body weight losses; and pathological examination 14-16 days later revealed bronchopneumonia and bronchiectasis in all 4 rats.

Rats also survived four and eight-hour exposure to saturated vapor (27 and 26 ppm nominal concentration) generated from a bubbler of HDI at room temperature, but showed similar, though less severe signs of toxicity. The only pathology observed at sacrifice was chronic gastritis, possibly caused by swallowing the vapor, in two of the rats exposed four hours.

In an attempt to define a no-effect concentration, rats were exposed four hours to saturated HDI vapor diluted by an additional two liters per minute air stream (11 ppm, nominal) and to 5 ppm, nominal, HDI delivered by a syringe drive. None of these animals showed tissue changes, but the rats in the 11 ppm exposure showed the same, though less severe, clinical signs of toxicity as rats at higher concentrations.

B. Subacute

Four male albino ChR-CD rats were exposed to room temperature saturated HDI vapor (average nominal concentration, 30 ppm), generated as described above in the acute exposures, four hours daily for ten days over a two-week period. A group of comparable control rats was exposed at the same time to a flow of two liters per minute dried air.

Two of the four HDI rats died, one during the eighth exposure, and the other six days after the tenth exposure. The condition of both had declined steadily.

Clinical signs of toxicity for all rats were similar to those observed in the rats exposed on an acute basis with respiratory impairment continuing between exposures. In addition, the rat dying six days after the tenth exposure was observed, on the fifth day after the exposure period, to have a slit-shaped opacity of the cornea of one eye.

The two surviving rats showed less severe clinical signs of toxicity, and appeared in better condition at the end of each treatment week than at the beginning. One of these, which had gained weight consistently from the seventh exposure day on, was sacrificed immediately after the tenth exposure, the other, ten days later. The latter rat did not show consistent weight gain until six days after the last exposure.

Pathological examination of the rat dying during the exposure period showed bronchitis with purulent obstruction of some bronchial branches. The rat dying six days after the exposure period had bronchopneumonia in addition to the corneal ulcer. The rat sacrificed immediately after the tenth exposure showed no pathology, the one sacrificed ten days later, bronchopneumonia. There was no pathology in control rats.

INHALATION IRRITANCY THRESHOLD STUDIES

Because the earlier studies with TDI showed that dogs responded dramatically with signs of eye, nose and throat irritation when exposed to analytical concentrations of only 1-2 ppm TDI for one-half to two hours, and because HDI appeared more irritating in tests described above than TDI, it seemed reasonable that similar dog exposures to analytical concentrations of HDI would assist in the comparison of the irritancy potential of the two chemicals. In addition, preliminary work comparing analytical HDI concentrations to nominal concentrations (those derived by weight loss) indicated a substantial difference between the two. For this reason, the results of animal exposure to analytical concentrations of HDI were also deemed necessary.

Accordingly, two female beagle dogs from the stock colony were exposed six times over a ten-day period to analytical concentrations of less than 2 ppm HDI. (length of exposure period not indicate

A weighed sample of HDI in a DeVilbiss nebulizer was placed inside a 10 cubic meter exposure chamber. The HDI spray from a measured volume of dried air was directed into a stream of pure air metered into the chamber through a one-half inch copper pipe, at a rate of 70 to 95 liters per minute. The HDI-air mixture was directed into a one liter beaker placed laterally about one foot from the nozzle of the nebulizer. Continuous air flows were maintained in the chamber during exposure.

Both the prime and maintenance levels of HDI concentration in the chamber were established experimentally before animal exposures were attempted.

Air samples, five to ten liters in volume, were drawn at 20-30 minute intervals, through Nylaflow tubing, from an area in the center of the chamber and about two feet from the floor. The analytical method described under Standardization I (see Appendix I) was used to determine the concentration of HDI. Table II summarizes analyses from dog exposures.

Results of this study indicated that both dogs experienced severe nose, throat, and eye irritation at all concentrations of HDI tested (0.27 to 1.43 ppm). Lacrimation, licking of noses, coughing up foamy material, and vomiting were observed, and dogs appeared agitated and uncomfortable, especially during the first exposures. The severity of these signs of irritation was correlated, in general, to the HDI concentration. Recovery was complete by the end of each exposure day, and no effects were observed on the dogs' rectal temperature, weight, or general condition.

For direct comparison, the same dogs were given an exposure to TDI at a low concentration, 11 days after the last HDI exposure. The TDI was vaporized and diluted with pure air under conditions identical to the HDI exposures.

Air samples from the exposure chamber were analyzed by two methods, described in detail by Marcali[5]. The diazometric method determines the concentration of TDI. The cellosolve-nitrite method determines both TDI and TDI urea which is formed from TDI in the presence of moisture. The results of the analyses (Table III) indicate that TDI urea was not present in the chamber atmosphere at a high enough concentration to affect the results. ~~a different~~ compound

Dogs showed lacrimation and licking of noses during this TDI exposure (0.46 ppm), as in the previous HDI exposures, with recovery the day of exposure. Eighteen days after the TDI exposure, the dogs were sacrificed and autopsied, with gross and microscopic examination of the major organs. No pathological change was observed which could be attributed to the test exposures. ~~structurally~~

Evaluation of this inhalation dog study is made difficult because: (1) the dogs appeared to learn, as the exposure period progressed, that lying quietly in the exposure chamber with their eyes closed decreased their discomfort; and 2) it was not possible to analyze for lower concentrations of HDI than those used (0.3 ppm), and hence, establishment of a maximum non-irritancy level was not possible. However, from these tests, no really significant differences in dog response to HDI and TDI were noted. Both compounds were found to be extreme eye and respiratory irritants at the lowest concentrations tested.

SUMMARY AND DISCUSSION

Results of these tests would indicate that HDI is more toxic orally and more irritating to the skin and mucous membrane tissue than TDI. They provided further evidence for Goldblatt's hypothesis that aliphatic isocyanates are more toxic than aromatics.

The oral ALD for HDI was found to be 1500 mg/kg for rats. Animals receiving lethal doses died in 2 to 21 hours, developing cyanosis, respiratory impairment, and diarrhea. Microscopic examination of tissues failed to reveal an anatomical cause of death. Animals receiving sublethal doses had transient weight loss, respiratory impairment, and diarrhea, which was evident in animals tested as low as 40 mg/kg. Examination of tissues at sacrifice revealed irritation to the stomach mucosa in rats receiving doses as low as 60 mg/kg.

Although the oral ALD of 1500 mg/kg would indicate that HDI has a low level of acute toxicity, the fact that it produced injury to the stomach in doses as low as 60 mg/kg emphasizes the extreme irritant properties of this chemical. It was considerably more toxic and more irritating to the stomach than TDI (ALD 7500 mg/kg - see Table I).

The subacute oral test on HDI was carried out at 300 mg/kg (5 per cent solution in peanut oil). Although rats lost weight, had diarrhea, and showed signs of irritation, they survived ten treatments. Examination of tissues revealed gastritis. No evidence of systemic toxicity was observed. The subacute oral test on TDI was carried out at 1500 mg/kg (50 per cent solution in peanut oil) and three of six rats died. In view of the differences in dose levels between HDI and TDI and the tenfold difference in concentrations of solutions administered, and the fact that both act primarily as irritants, it is not possible to draw direct comparisons as to the potential cumulative toxicity of the two compounds.

HDI is a strong irritant for guinea pig skin producing moderate irritation in concentrations as low as 0.5 per cent as compared to only occasional mild irritation for 0.5 per cent TDI. Like TDI, HDI is a strong sensitizer.

HDI was markedly irritating to the conjunctiva of rabbit eyes and produced permanent damage to the cornea. Prompt washing of the eye did not seem to appreciably decrease the lesions. TDI produced less severe conjunctival irritation than HDI and only transient corneal damage.

HDI, like TDI, is much more toxic by inhalation than when given orally. A four-hour exposure of rats to 72 ppm caused severe respiratory impairment. An average concentration of 370 ppm caused death within 2-3 hours. Extreme irritation of the type produced by HDI can cause laryngeal spasm and death. This was believed to be the case here, because of the nature of the gasping, and since the pulmonary damage was not sufficient per se to cause death. The respiration of rats was affected down to and including the 11 ppm exposure (nominal).

Two of four rats, exposed four hours per day for ten days over a two-week period to room temperature saturated HDI vapor (30 ppm nominal concentration), died, one during the eighth exposure and one six days after the exposure period. Clinical signs of toxicity were similar to those of rats exposed acutely. Examination of the tissues of these rats showed three of the four had bronchopneumonia. Qualitatively, the results were similar to those observed for TDI; but due to the difference in methods of exposure, quantitative comparisons are difficult to draw.

It is inconceivable that any human being would voluntarily inhale such irritating vapors for so long. However, the results of this test do point out the hazard of chronic irritation of the respiratory tract, leading to bronchial infection, from repeated exposure to HDI vapor. Similar results were found for TDI.

Since the irritation factor in the toxicity of these compounds is so much greater than the systemic toxicity, any safe levels established should be based on the former. It was hoped that comparative concentration figures could be obtained using dogs as test animals. However, inability to obtain accurate analyses below 0.3 ppm prevented the actual determination of a no-effect level for dogs for either compound. It can be said that the average concentrations of 0.28 ppm of HDI and 0.46 ppm of TDI produced roughly comparable visible irritation.

Another factor to consider in evaluating HDI toxicity is the report of asthmatic reactions in some humans accidentally exposed to TDI and other organic isocyanates. In view of the skin sensitization produced by both HDI and TDI, allergic asthmatic reaction in humans exposed to HDI should be considered likely.

RECOMMENDATIONS

On the basis of the severe skin, eye and mucous membrane irritation produced by HDI and TDI, skin and eye contact and ingestion of these materials must be avoided.

A threshold limit of 0.02 ppm will probably be re
TDI by the American Conference of Governmental Industrial
their 1961 meeting. The advisability of using a smaller fig
due to its somewhat greater irritancy becomes strictly acaden
time in view of the lack of an analytical method of sufficien
tivity in this range. Inhalation exposure to both compounds s
avoided since acute exposure can lead to acute irritation of t
tract, and repeated exposures can cause chronic irritation lead
chial infection. The possibility of asthmatic reaction also exi
both compounds.

HASKELL LABORATORY FOR TOX
AND INDUSTRIAL MEDICI

Report by: Eleanor E. Hurlbrink
Eleanor E. Hurlbrink

Approved by: D. B. Hood
D. B. Hood
Chief, Toxicology Section

John A. Zapp, Jr.
Director

EEH:emh
March 16, 1961
Report No. 9-61

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ- 1092 -12000 SEQ. A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: E. I. Dupont de Nemours and Company

SUB. DATE: 10/15/92 OTS DATE: 10/27/92 CSRAD DATE: 02/22/95

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0634) REFER TO CHEMICAL SCREENING
(0678) CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/USERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

CHEMICAL NAME:

CAS#
822-06-0
584-84-9

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
0202	ONCO (ANIMAL)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
(0212)	ACUTE TOX. (ANIMAL)	01 02 04
(0213)	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
0215	CHRONIC TOX (ANIMAL)	01 02 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
(0228)	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

TRIAGE DATA:

NON-CBI INVENTORY
(YES)
CAS SR
NO
(IN TRIAGE)

ONGOING REVIEW
YES (DROP/REFER)
NO (CONTINUE)
REFER

SPECIES
RAT
GP
Dog

TOXICOLOGICAL CONCERN:
LOW
MED
(HIGH)

USE:

PRODUCTION:

COMMENTS:

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

APR 18 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan

Terry R. O'Bryan
Risk Analysis Branch

Enclosure 12000A

Triage of 8(e) Submissions

Date sent to triage: APR 20 1995 NON-CAP (CAP)

Submission number: 120201A TSCA Inventory: (Y) N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

(ATOX) (SBTOX) (SEN) w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX	CTOX	EPI	RTOX	GTOX
STOX/ONCO	CTOX/ONCO	IMMUNO	CYTO	NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

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entire document: (0) 1 2 **pages** 1 1st TAB **pages** 1, TABS

Notes:

Contractor reviewer : PML **Date:** 3/29/95

8(E)-12000A

L/L/H/H/H/M/H/L

ACUTE ORAL TOXICITY IN CD MALE ALBINO RATS IS OF LOW CONCERN BASED ON AN LD50 BETWEEN 1000 MG/KG AND 1500 MG/KG. DOSAGES (GAVAGE) AND MORTALITY DATA ARE AS FOLLOWS: EACH DOSE FROM 12 TO 1000 MG/KG, WITH A FACTOR OF 1.5 BETWEEN DOSE LEVELS (0/1 PER DOSE); 1500 MG/KG (1/1); 2250 MG/KG (1/1); AND 3400 MG/KG (1/1). AT LETHAL DOSES, TOXIC SIGNS INCLUDED PALLOR, CYANOSIS, AND SLOW AND DEEP BREATHING AND DIARRHEA. SURVIVORS LOST WEIGHT INITIALLY. AT 1000 MG/KG AND LOWER, CLINICAL SIGN INCLUDED WEIGHT LOSS, RESPIRATORY IMPAIRMENT, AND DIARRHEA.

SUBACUTE ORAL TOXICITY IN CD MALE RATS IS OF LOW CONCERN. DOSAGE (GAVAGE, 10-DAYS) AND MORTALITY DATA ARE AS FOLLOWS: 300 MG/KG (0/6). TOXIC SIGNS INCLUDED DIARRHEA AND SALIVATION. RATS SACRIFICED ON DAY 10 SHOWED ULCERATIVE GASTRITIS. RATS SACRIFICED TEN DAYS LATER SHOWED A HEALING GASTRITIS.

ACUTE DERMAL IRRITATION IN MALE GUINEA PIGS IS OF HIGH CONCERN BASED ON NECROSIS FROM EXPOSURE TO THE NEAT TEST SUBSTANCES, SEVERE ERYTHEMA AND EDEMA FROM A 25% SOLUTION, MODERATE IRRITATION FROM A 0.5% SOLUTION, AND NO EFFECT FROM A 0.05% SOLUTION ON INTACT SKIN. VOLUMES WERE NOT INDICATED.

DERMAL SENSITIZATION IN GUINEA PIGS IS OF HIGH CONCERN. NINE APPLICATIONS OF 0.5 TO 0.05 PER CENT SOLUTIONS TO ABRADED SKIN OVER A PERIOD OF THREE WEEKS WERE FOLLOWED BY A THREE-WEEK REST PERIOD. CHALLENGE TESTS AT THE END OF THE REST PERIOD SHOWED THAT 8/9 GUINEA PIGS HAD DEVELOPED ALLERGIC CONTACT DERMATITIS.

ACUTE EYE IRRITATION IN MALE ALBINO RABBITS IS OF HIGH CONCERN BASED ON SEVERE CONJUNCTIVAL INFLAMMATION, AND SEROUS AND HEMORRHAGIC EXUDATE IN BOTH EYES, AND SEVERE (UNWASHED) AND MODERATE (WASHED) CORNEAL INJURY FROM EXPOSURE TO 0.1 ML. AFTER EXPOSURE, PATHOLOGY REVEALED HEALED CORNEAL LESIONS AND INFLAMMATION OF THE EYELIDS (UNWASHED).

ACUTE INHALATION TOXICITY IN MALE ALBINO CD RATS IS OF ~~MEDIUM~~ low CONCERN. 4 RATS AT A TIME WERE EXPOSED FOR 4- OR 8-HOURS TO TEST SUBSTANCE. NO TREATMENT RELATED MORTALITIES OCCURRED. TOXICITY SIGNS INCLUDED LABORED BREATHING AND GASPING. SEVERE WEIGHT LOSS WAS OBSERVED POST TREATMENT. PATHOLOGICAL SIGNS INCLUDED BRONCHOPNEUMONIA AND BRONCHIECTASIS.

SUBACUTE INHALATION TOXICITY IN MALE ALBINO CD RATS IS OF HIGH CONCERN BASED ON MORTALITY (2/4). DOSAGE (4-HOURS/DAY FOR 10-DAYS) WAS 30 PPM. PATHOLOGY REVEALED BRONCHITIS AND OBSTRUCTION OF SOME BRONCHIAL BRANCHES AND A CORNEAL ULCER.

SUBACUTE INHALATION TOXICITY IN FEMALE BEAGLE DOGS IS OF LOW CONCERN BASED ON COMPLETE RECOVERY AT THE END OF EACH EXPOSURE DAY AND NO EFFECTS OBSERVED ON DOGS' RECTAL TEMPERATURES, WEIGHT, OR

GENERAL CONDITION. THE TEST ANIMALS WERE EXPOSED 6 TIMES OVER A TEN-DAY PERIOD TO ANALYTICAL CONCENTRATIONS OF LESS THAN 2 PPM OF HDI (LENGTH OF EXPOSURE PERIOD WAS NOT INDICATED). CLINICAL SIGNS OF TOXICITY INCLUDED SEVERE NOSE, THROAT, AND EYE IRRITATION AT ALL CONCENTRATIONS (0.27 TO 1.43 PPM). LACRIMATION, LICKING OF NOSES, COUGHING UP FOAMY MATERIAL, AND VOMITING WERE OBSERVED. THE SAME DOGS WERE EXPOSED TO TDI AT A LOW CONCENTRATION, 11 DAYS AFTER THE LAST HDI EXPOSURE. DOGS SHOWED LACRIMATION AND LICKING OF NOSES DURING THIS TDI EXPOSURE (0.46 PPM). NO PATHOLOGICAL CHANGE WAS NOTED.